

Development of Induced Pluripotent Stem Cells for Modeling Human Disease

Grant Award Details

Development of Induced Pluripotent Stem Cells for Modeling Human Disease

Grant Type: New Cell Lines

Grant Number: RL1-00649

Investigator:

Name: Fred Gage

Institution: Salk Institute for Biological Studies

Type: PI

Disease Focus: Amyotrophic Lateral Sclerosis, Autism, Blood Disorders, Neurological Disorders, Pediatrics, Rett's Syndrome

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: \$1,737,720

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 2

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Reporting Period: Year 3

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Grant Application Details

Application Title:

Development of Induced Pluripotent Stem Cells for Modeling Human Disease

Public Abstract:

Human embryonic stem cells (hESC) hold great promise in regenerative medicine and cell replacement therapies because of their unique ability to self-renew and their developmental potential to form all cell lineages in the body. Traditional techniques for generating hESC rely on surplus IVF embryos and are incompatible with the generation of genetically diverse, patient or disease specific stem cells. Recently, it was reported that adult human skin cells could be induced to revert back to earlier stages of development and exhibit properties of authentic hESC cells. The exact method for "reprogramming" has not been optimized but currently involves putting multiple genes into skin cells and then exposing the cells to specific chemical environments tailored to hESC cell growth. While these cells appear to have similar developmental potential as hESC cells, they are not derived from human embryos. To distinguish these reprogrammed cells from the embryonic sourced hESC cells, they are termed induced pluripotent stem (iPS) cells. Validating and optimizing the reprogramming method would prove very useful for the generation of individual cell lines from many different patients to study the nature and complexity of disease. In addition, the problems of immune rejection for future therapeutic applications of this work will be greatly relieved by being able to generate reprogrammed cells from individual patients. We have initiated a series of studies to reprogram human and mouse fibroblasts to iPS cells using the genes that have already been suggested. While induction of these genes in various combinations have been reported to reprogram human cells, we plan to optimize conditions for generating iPS cells using methods that can control the level of the "reprogramming" genes, and also can be used to excise the inducing genes once reprogramming is complete; thus avoiding unanticipated effects on the iPS cells. Once we have optimized the methods of inducing human iPS cells from human fibroblasts, we will make iPS cells from patients with 2 different neurological diseases. We will then coax these iPS cells into specific types of neurons using methods pioneered and established in our lab to explore the biological processes that lead to these neurological diseases. Once we generate these cell based models of neural diseases, we can use these cells to screen for drugs that block the progress, or reverse the detrimental effects of neural degeneration. Additionally, we will use the reprogramming technique to study models of human blood and liver disease. In these cases, genetically healthy skin cells will be reprogrammed to iPS cells, followed by introduction of the deficient gene and then coaxed to differentiate into therapeutic cell types to be used in transplantation studies in animal models of these diseases. The ability of the reprogrammed cell types to rescue the disease state will serve as a proof of principle for therapeutic grafting in

**Statement of Benefit to
California:**

It has been close to a decade since the culture of human embryonic stem (hES) cells was first established. To this day there are still a fairly limited number of stem cell lines that are available for study due in part to historic federal funding restrictions and the challenges associated with deriving hES cell lines from human female egg cells or discarded embryos. In this proposal we aim to advance the revolutionary new reprogramming technique for generating new stem cell lines from adult cells, thus avoiding the technical and ethical challenges associated with the use of human eggs or embryos, and creating the tools and environment to generate the much needed next generation of human stem cell lines. Stem cells offer a great potential to treat a vast array of diseases that affect the citizens of our state. The establishment of these reprogramming techniques will enable the development of cellular models of human disease via the creation of new cell lines with genetic predisposition for specific diseases. Our proposal aims to establish cellular models of two specific neurological diseases, as well as developing methods for studying blood and liver disorders that can be alleviated by stem cell therapies. California has thrived as a state with a diverse population, but the stem cell lines currently available represent a very limited genetic diversity. In order to understand the variation in response to therapeutics, we need to generate cell lines that match the rich genetic diversity of our state. The generation of disease-specific and genetically diverse stem cell lines will represent great potential not only for CA health care patients but also for our state's pharmaceutical and biotechnology industries in terms of improved models for drug discovery and toxicological testing. California is a strong leader in clinical research developments. To maintain this position we need to be able to create stem cell lines that are specific to individual patients to overcome the challenges of immune rejection and create safe and effective transplantation therapies. Our proposal advances the very technology needed to address these issues. As a further benefit to California stem cell researchers, we will be making available the new stem cell lines created by our work.

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